REMARKS

I. INTRODUCTION

In response to the Office Action dated March 28, 2006, claims 17 and 38 have been amended. Claims 17-35 and 37-44 remain in the application. Entry of these amendments, and reconsideration of the application, as amended, is requested.

II. CLAIM AMENDMENTS

Applicants' attorney has made amendments to the claims as indicated above. These amendments were made solely for the purpose of clarifying the language of the claims, and do not introduce new matter or raise new issues. These amendments are offered in accordance with a suggestion made by the Examiner in a telephone conference on March 10, 2005.

III. EXAMINER INTERVIEW

Record is made of a telephonic interview April 4, 2005, between Applicants' attorney, Karen Canady, and Examiners Katcheves and Ketterer, in connection with the present patent application. During this interview, discussion centered on reconsideration of the evidence previously submitted in support of enablement. Although previously it had been ageed that the evidence already of record should suffice to overcome the enablement rejection, it appears from the most recent Office Action that not all evidence of record has been considered. To clarify the support for enablement, Applicants discuss the evidence below.

IV. ENABLEMENT REJECTION

At pages 2-5 of the Office Action, the rejection of claims 17-35 and 37-44 under 35 U.S.C. §112, first paragraph, was maintained. The rejection was based on reasons of record and an alleged lack of enabling disclosure provided by the specification. Applicants respectfully traverse this rejection and maintain that the extensive evidence already of record establishes that the application as originally filed teaches one skilled in the art how to make and use the claimed invention. Although extensive data have been presented in previous responses, all of which contribute to

supporting enablement of the claimed invention, Applicants highlight below select portions of these data showing the successes achieved with small fragment homologous replacement (SFHR) of the invention.

Although the Declaration under 37 CFR §1.132 by Dr. Dieter Gruenert was acknowledged at page 2 of the Office Action, the ***in vivo* evidence of successful therapeutic application** of the invention described at paragraph 6 of this Declaration appears to have been overlooked. Because such a large volume of evidence has been provided (and is already of record) to support enablement of the claimed subject matter, Applicants submit herewith a **Table of Evidence Supporting Enablement**. This Table should help the Examiner ensure that all pieces of evidence have been considered. As shown by the Table, data have been provided to show success with *in vivo, ex vivo* and *in vitro* delivery methods, using lipofectamine, microinjection and dendrimer as the delivery vehicle, all of which are supported by the application as originally filed.

The Examiner is requested to review in particular the "Result" column of the Table for a summary of the many aspects of the claimed subject matter that are supported by these data. The evidence establishes that the small fragment homologous replacement (SFHR) method of the invention successfully and stably replaces the target region of genomic DNA with the replacement fragment, in the correct location, and in a manner that permits successful mRNA expression and functional correction (e.g. correction of the mutation that disrupts chloride transport in respiratory epithelium in cystic fibrosis such that normal ion transport is restored).

In addition, cells that have been corrected *ex vivo* have been shown to exhibit fragment replacement at both alleles, with sufficient levels of gene conversion to support therapeutic benefit, and can be engrafted into host animals. This study by Prokopishyn et al. has been previously disregarded by the Examiner because the host animals were immune deficient mice (NOD/SCID mice and also N/Sβ2mk/o mice). The Examiner is respectfully requested to reconsider these data in view of: (1) the engrafted cells were human umbilical cord blood stem/progenitor cells, an attractive target cell that is xenogeneic with respect to available host experimental subjects; and (2) the SFHR method of the invention is attractive because it is **LESS likely to raise problems of immune rejection** since it obviates the need to use xenogeneic materials, as no viral, plasmid or other foreign vectors are required, and the cells to be grafted can be derived from the same subject

to which the therapeutic method would be applied.

The Examiner is respectfully reminded that other gene therapy systems have had immune response problems related to the use of cDNA and viral-based vectors, neither of which is used in the SFHR method of Applicants' claims. Even if the Prokopishyn study cannot address questions relating to immune rejection, no reasoning has been provided to support the assumption that host immune problems observed in other gene therapy models that do require foreign genetic material are applicable to the presently claimed method. In addition, the Examiner's statement at page 3 of the Office Action, that the data "fails to lack of direction on how to ensure that cells from the *ex vivo* method would replace, or otherwise out-compete, the endogenous defective cells" contradicts the discussion at page 6 o f the Prokopishyn manuscript, which states:

> Based on bone marrow transplantation studies, as few as 10% normal peripheral donor blood cells ($\beta^A\beta^A$) will dramatically improve the health of sickle patients [citations omitted]. Since under normal conditions, cells from sickle cell trait patients ($\beta^S\beta^A$) are function, transplanted cells modified at only one allele may also have therapeutic benefit. Thus, the level of gene conversion achieved in this study could be of therapeutic benefit in patients with sickle cell disease, provided that the converted cells were maintained at significant frequency in the marrow of transplant recipients. Since the corrected mature red blood cells have prolonged survival advantage over sickle cells, it is possible that the percentage of corrected marrow stem cells that are required will be <10%.

It is further noted that Prokopishyn et al. reported successful conversion in a significant portion of experimental samples (page 5, paragraph 2). Moreover, *ex vivo* methods allow for multiple administrations to increase the population of corrected cells. The authors also observed gene conversion 3-5 weeks after microinjection, or after 8-12 cell doublings, indicating that SFHR-mediated changes were being passed on to subsequent generations. Accordingly, the Examiner is urged to consider the remarkable accomplishments demonstrated by these data.

At page 5 of the Office Action, the Examiner once again alleges, incorrectly, that none of the delivery vehicles used in Exhibit C were taught or suggested in the instant specification. This statement is not true. As Applicants have repeatedly pointed out, and as reiterated in the Declaration by Dr. Gruenert (see paragraph 7), **Lipofectamine as a delivery vehicle is explicitly**

taught in the specification at page 42, line 11 (discussing the data presented in Figure 13). In addition, lipid-based delivery systems (including dendrimers) are taught throughout the specification (at pages 24-25, at page 73, line 12, and at page 75, line 32, to page 76, line 14).

Accordingly, Applicants respectfully request the Examiner reconsider the entire record, including all of the evidence summarized in the Table submitted herewith as well as the teachings and examples provided in the specification.

V. ADDITIONAL ISSUES

During the telephonic interview of April 4, 2005, the Examiners indicated that additional prior art may be cited in a forthcoming further Office Action. Should the Examiner be reviewing additional prior art pursuant to an updated search, the Examiner is respectfully requested to consider the following. The nature of the references alluded to during the telephonic interview appear to be cumulative (if not duplicative) of references already considered during the examination of the claimed invention. Applicants note that the claimed invention requires the replacement DNA fragment consist essentially of flanking noncoding sequence adjacent to each of the 3' and 5' ends of the at least one replacement exon, wherein the flanking noncoding sequence is homologous to and anneals to a 3' flanking noncoding sequence adjacent to the target fragment.

As stated previously (see Amendment submitted September 26, 2003), independent claims 17 and 37 have retained the phrase "consisting essentially of" in the preamble in connection with the phrase "replacement DNA fragment". MPEP §2111.03 states that the "transitional phrase 'consisting essentially of' limits the scope of a claim to the specified materials or steps 'and those that do not materially affect the basic and novel characteristic(s)' of the claimed invention" (citing *in re Herz*, 537 F.2nd 549, 551-552, 190 USPQ 461, 463 (CCPA 1976), *emphasis in original*). It is improper to disregard the distinction between the transitional phrases "comprising" and "consisting essentially of".

Applicants have stated for the record that the basic and novel characteristics of the claimed invention involves use of small fragments for targeted replacement of a gene in a cell which relies on use of flanking noncoding sequence in the exogenous replacement fragment that is homologous to and anneals to flanking noncoding sequence of the target fragment in the gene of the cell. This

statement is supported by the specification, for example, at page 22, lines 3-11. Accordingly, the transitional phrase "consisting essentially of", as used in claims 17 and 37, indicates that additional material beyond the flanking noncoding sequence of the replacement fragment would materially affect the basic and novel characteristics of the claimed invention. It would therefore be improper to construe "consisting essentially of" as meaning "comprising" or as encompassing a replacement fragment that includes an entire genomic sequence, for example, or is flanked by an additional exon (and/or by foreign vector sequence) that is not flanked by noncoding sequence.

The prior art did not teach or suggest the composition or method of small fragment homologous replacement using replacement DNA fragments having the features recited in Applicants' claims.

VI. CONCLUSION

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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